Implementation research needs on malaria vaccine delivery according to epidemiological context

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How people can get access to vaccines?

Usual

Expanded Program on Immunization

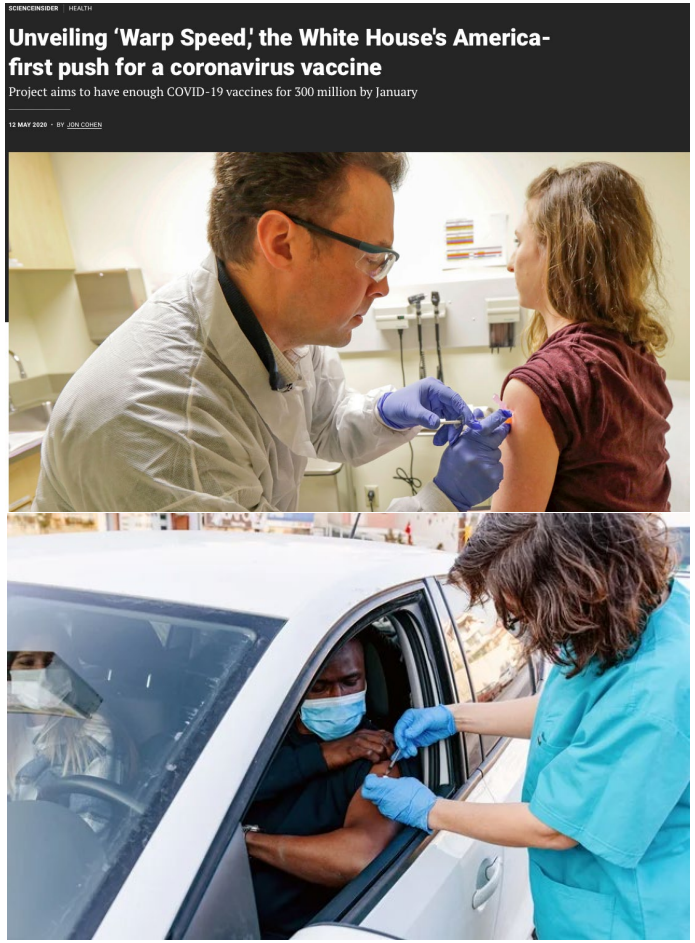
BURKINA FASO
Unité - Progrès - Justice

CALENDRIER VACCINAL DE L'ENFANT DE 0 A 23 MOIS

Age	Vaccins	Maladies cibles
Naissance	BCG	Tuberculose
	VPO 0	Poliomyélite
	HepB	Hepatite B
02 mois	DTC- HepB- Hib 1 (Penta1)	Diphtérie ,Tétanos, Coqueluche,Hépatite B, Hémophilius Influenzae b,
	VPO 1	Poliomyélite
	Pneumo 1 (PCV13)	Infection à Pneumocoques (13 sérotypes) dose 1
	Rota 1	Diarrhée à Rota virus
03 mois	DTC-HepB-Hib2 (Penta2)	Diphtérie, Tétanos, Coqueluche, Hépatite B, Hémophilius Influenzae b,
	VPO 2	Poliomyélite
	Rota 2	Diarrhée à Rota virus
04 mois	DTC-HepB-Hib3 (Penta3)	Diphtérie ,Tétanos, Coqueluche, Hépatite B, Hémophilius Influenzae b,
	VPO 3	Poliomyélite
	Pneumo 2 (PCV 13)	Infection à Pneumocoque (13 sérotypes) dose 2
	Rota 3	Diarrhée à Rota virus
	VPI	Poliomyélite
09 mois	RR1	Rougeole +Rubéole
	VAA	Fièvre jaune
	Pneumo 3 (PCV 13)	Infection à Pneumocoques (13 sérotypes) dose 3
	VPI 2	Poliomyélite
15 mois	RR2	Rougeole + Rubéole
	MenA (MenAfriVac)	Méningite

Unusual

"Warp speed" for Covid-19 vaccination in the US



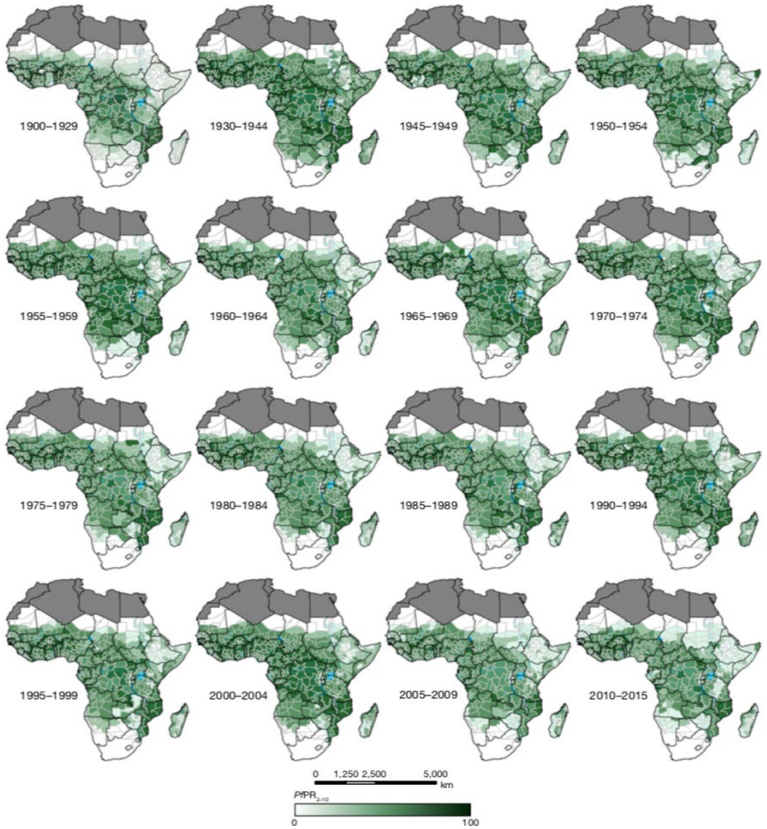
Very unusual

Polio vaccination in Pakistan 2019

Why epidemiological context matters in malaria endemic settings ?

Malaria transmission varies according to time and geography

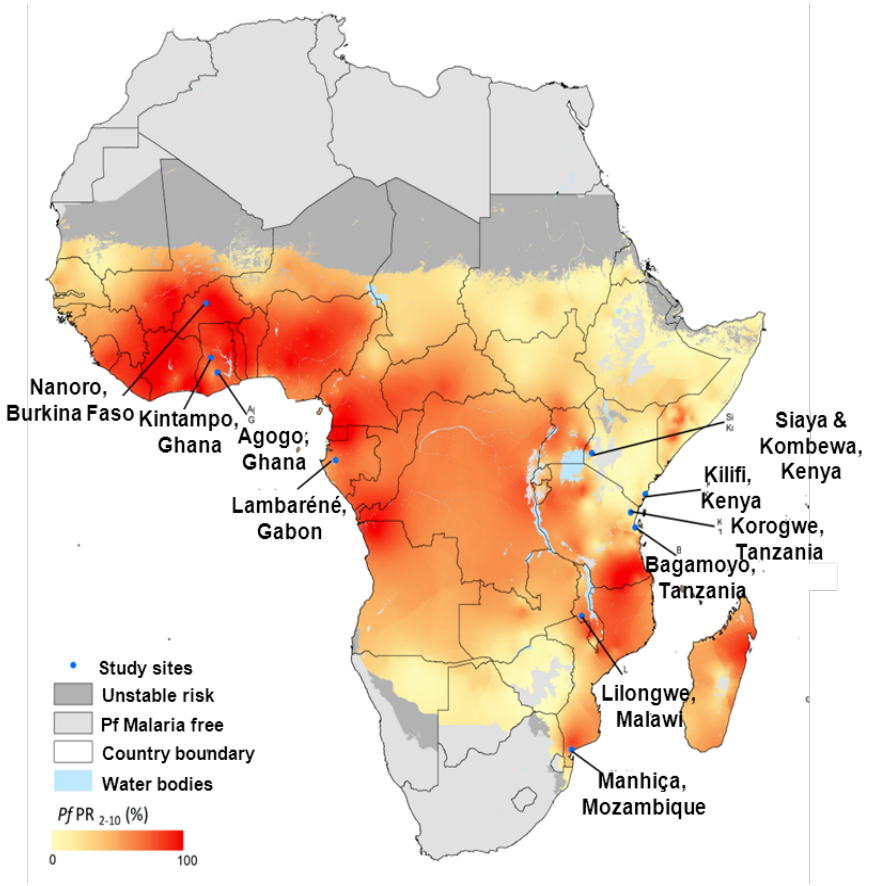
Almost homogenous



Changing spatial patterns of *P. falciparum* endemicity in sub-Saharan Africa 1900-2015

Snow *et al.* 2017 : ***Nature***

However



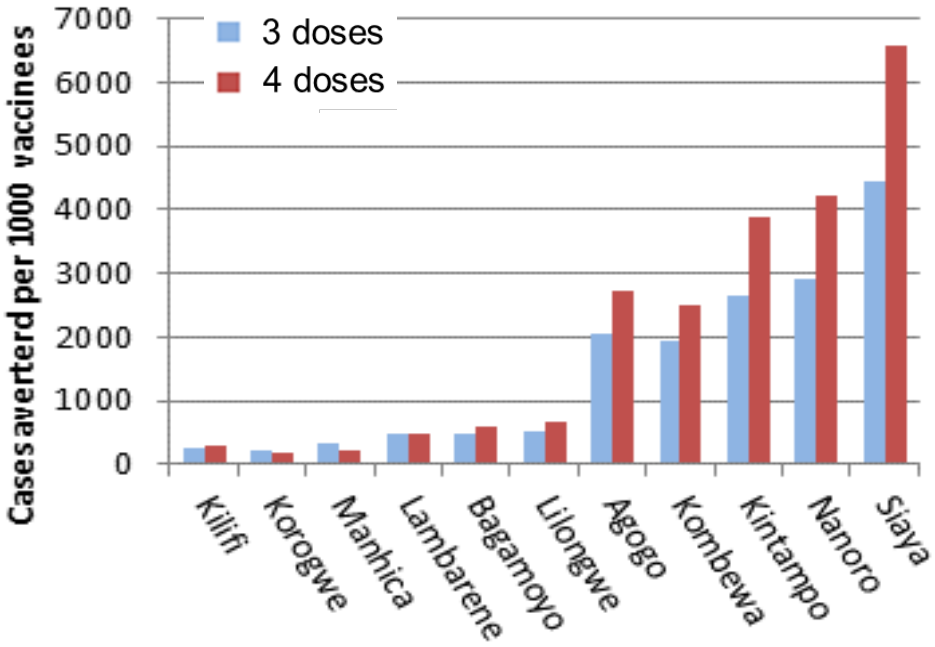
Trial sites of the RTS,S-AS01 Phase III multicenter efficacy trial

Why epidemiological context matters in malaria endemic settings ?

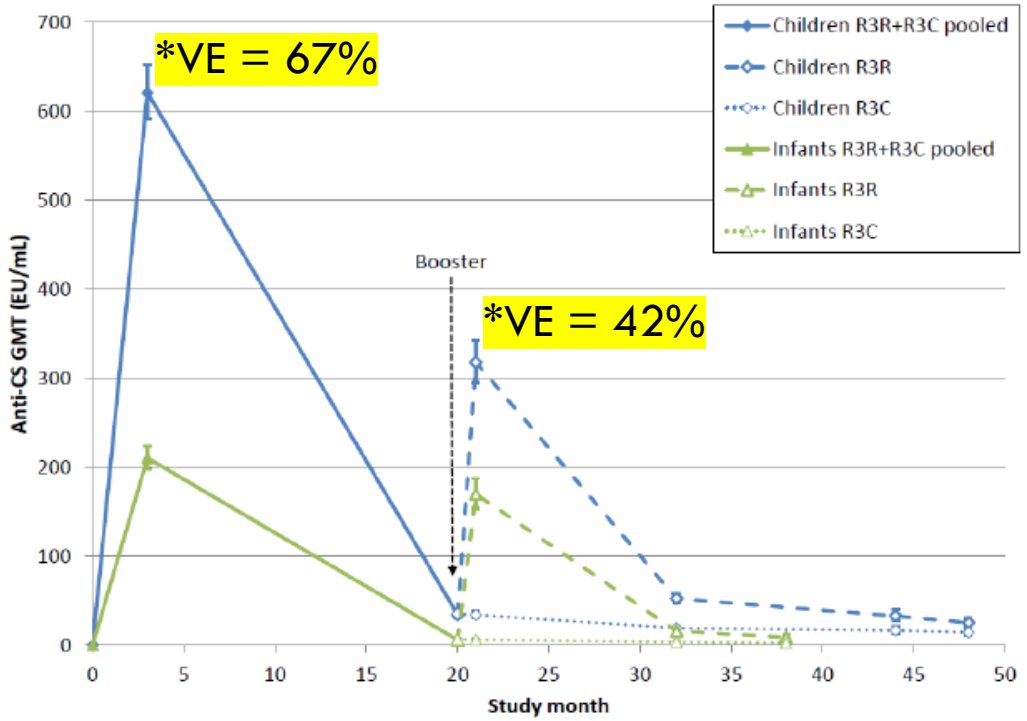
The case of RTS,S

39% **Reduction in clinical malaria**

29% **Reduction in severe malaria**



Number of clinical malaria cases averted with 3 or 4 doses among 5-17 months old children by study



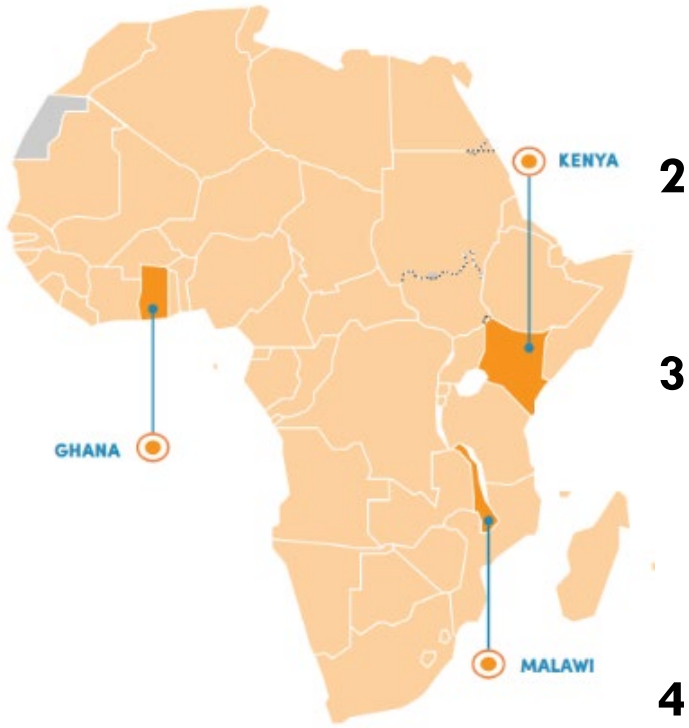
Anti-CS geometric mean titers in phase 3 trial

*VE : corresponding vaccine efficacy 6 months after dose 3 and 4

What about:

- Feasibility of reaching children with 4th doses
- Safety, emphasis on safety signals in Phase 3 trial
- Impact in routine use

WHO recommended a pilot implementation research in 2016



Summary findings from the implementation research

1. **Feasibility:** The first 3 doses of RTS,S can be delivered through EPI with high coverage (**60-70%**) though it requires an expanded schedule **(month 5, 6, 7, 8, 9)**

2. **Safety:** The vaccine is safe; no safety signals identified after over 3 million doses provided

3. **Impact:** The vaccine introduction resulted in a substantial reduction in severe malaria and all cause mortality :
   - 30% (95%CI 8%, 46%) reduction in hospitalized severe malaria
   - ~ 8% Reduction in all-cause mortality

4. **Equity:** the vaccine is reaching children who are not using other forms of prevention such as insecticide-treated nets, increasing access to malaria prevention interventions to > 61-75%

WHO recommended the first malaria vaccine (RTS,S) for children: Oct 2021

Missing information from the RTS,S pilot implementation

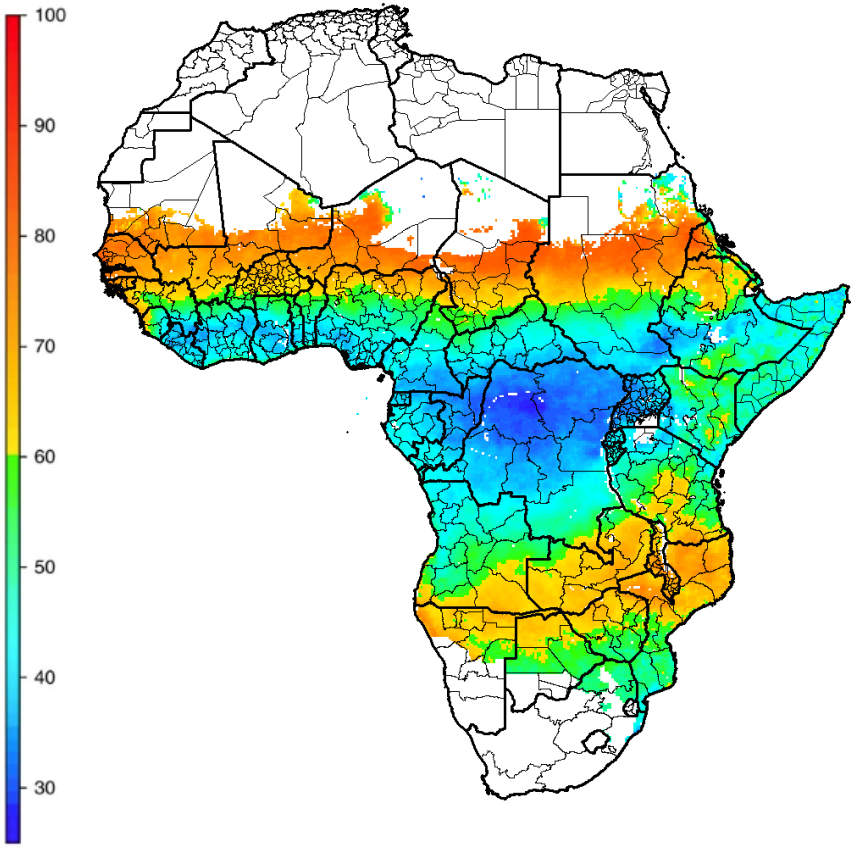
RTS,S was integrated into the childhood immunization schedule

Child Age / Vaccine/1	Birth	6 wks	10 wks	14 wks	5 mo	6 mo	7 mo	9 mo	12 mo	18 mo	22 mo	24 mo
BCG	1											
Oral polio	0	1	2	3								
DTP-HepB-Hib (penta)		1	2	3								
Pneumococcal conj.		1	2	3								
Rotavirus		1	2									
Inactivated Polio				1								
Meningococcal A conj.										1		
Measles-Rubella								1		2		
Yellow Fever								1				
RTS,S in Ghana						1	2	3				4
RTS,S in Kenya						1	2	3				4
RTS,S in Malawi					1	2	3				4	
Vitamin A						1			2	3		4
Growth Monitoring	●	●	●	●	●	●	●	●	●	●	●	●
Deworming												●

In areas of perennial malaria transmission, vaccine can be given with some flexibility to optimize delivery

- **What about areas with low EPI coverage ?**

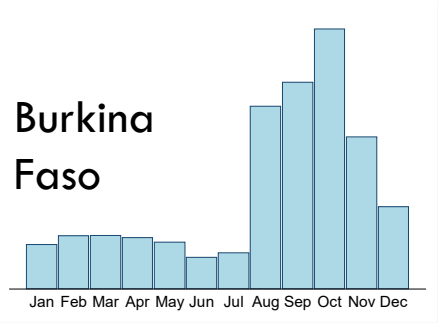
Seasonality of rainfall in Sub-saharan Africa

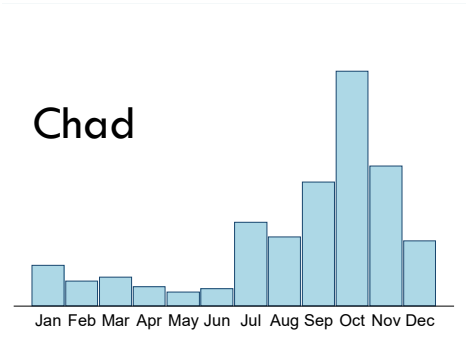


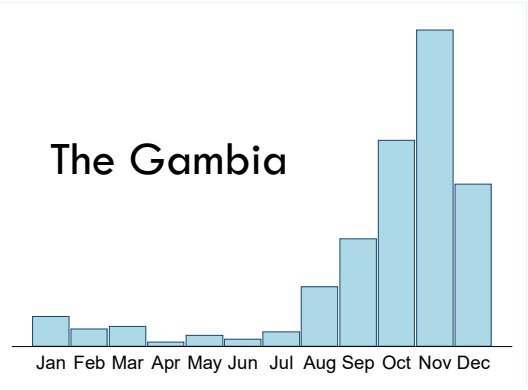
Cairns et al., Nature Comms 2012;3:881

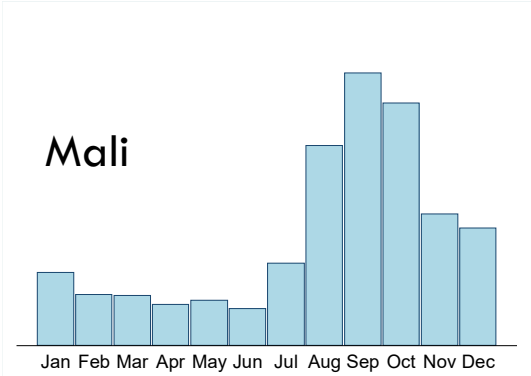
What about seasonal malaria transmission settings ?

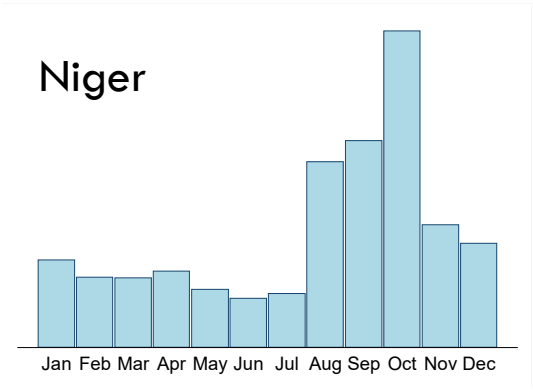
The seasonality of malaria in the African sahel and sub-sahel

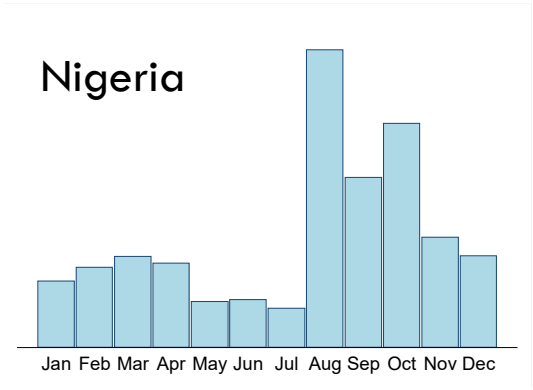


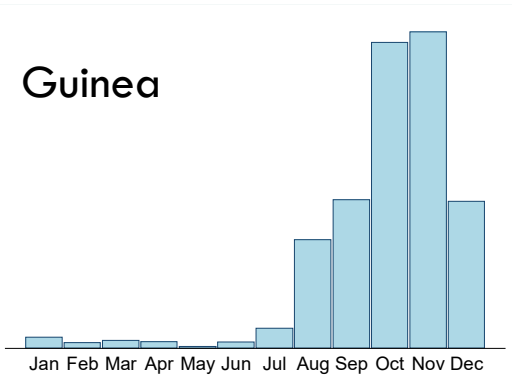


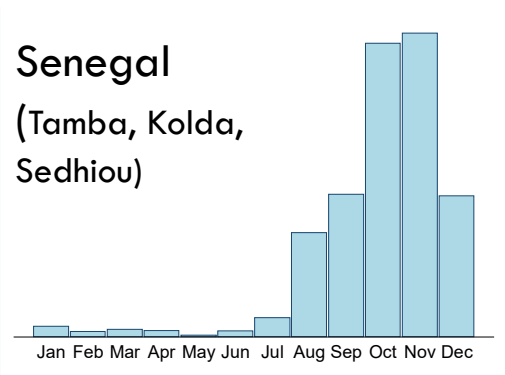








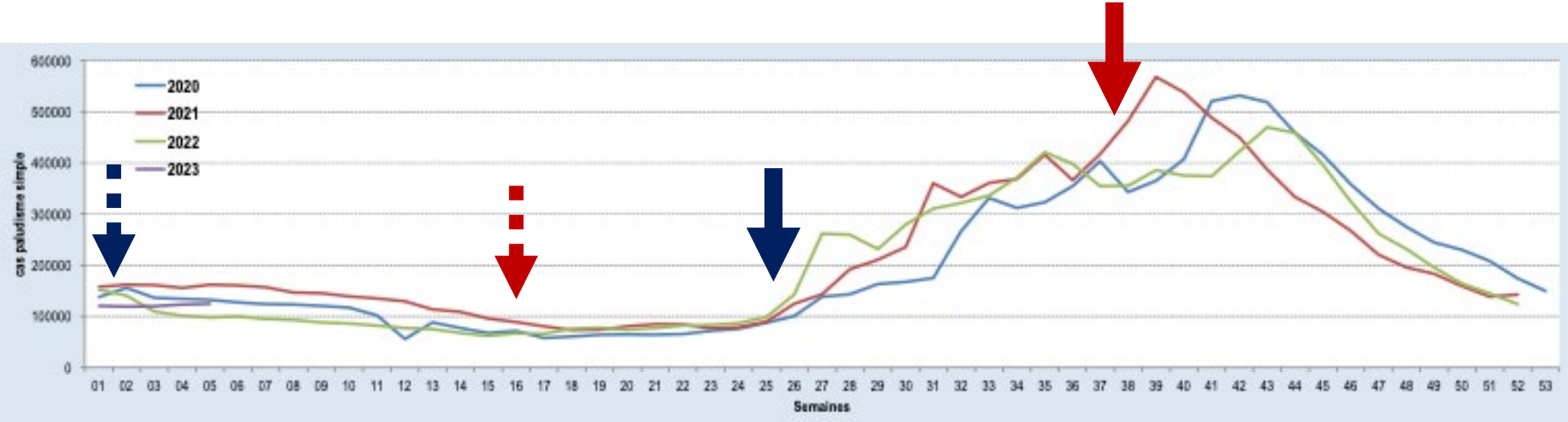




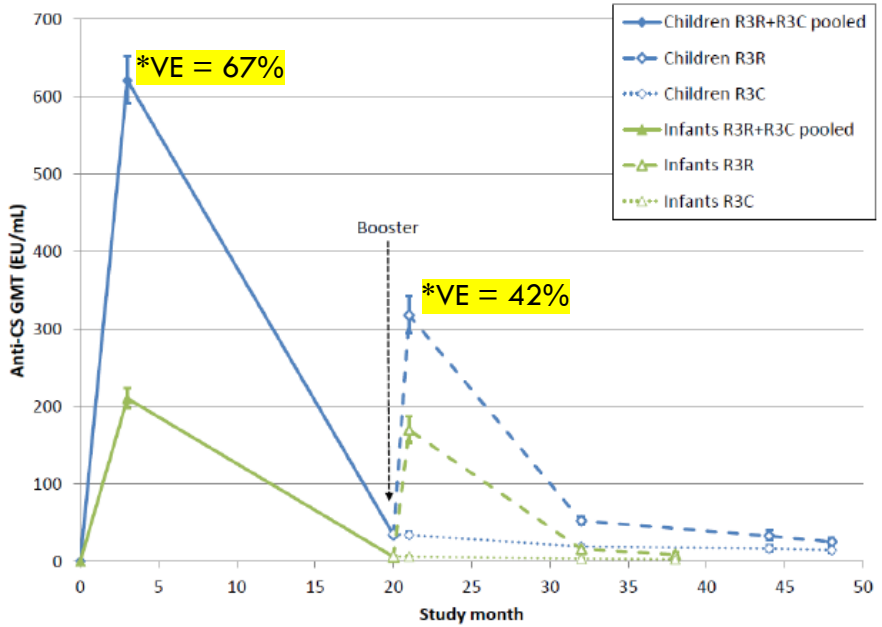
ACCESS SMC
Achieving catalytic expansion of seasonal malaria chemoprevention in the Sahel

Rationale for seasonally-targeted vaccination

Weekly records of malaria cases in Burkina Faso



RTS,S induced antibody titers evolution



When to vaccinate in order to have the highest impact ?

In areas with highly seasonal malaria transmission or areas with perennial malaria transmission with seasonal peaks, a seasonal vaccination approach should be considered

How best to deliver malaria vaccine in areas with seasonal transmission or perennial transmission with seasonal peaks ?

Greenwood *et al. Malar J (2017) 16:182*
DOI 10.1186/s12936-017-1841-9

Malaria Journal

REVIEW Open Access

Seasonal vaccination against malaria: a potential use for an imperfect malaria vaccine

Brian Greenwood[1*], Alassane Dicko[2], Issaka Sagara[2], Issaka Zongo[3], Halidou Tinto[3], Matthew Cairns[4], Irene Kuepfer[1], Paul Milligan[4], Jean-Bosco Ouedraogo[3], Ogobara Doumbo[2] and Daniel Chandramohan[1]

Abstract

In many parts of the African Sahel and sub-Sahel, where malaria remains a major cause of mortality and morbidity, transmission of the infection is highly seasonal. Seasonal malaria chemoprevention (SMC), which involves administration of a full course of malaria treatment to young children at monthly intervals during the high transmission season, is proving to be an effective malaria control measure in these areas. However, SMC does not provide complete protection and it is demanding to deliver for both families and healthcare givers. Furthermore, there is a risk of the emer-

RTS,S can be delivered in combination with other implemented malaria control tools such as, SMC, IPTi, bed nets distribution, and vitamin A or deworming campaigns ….

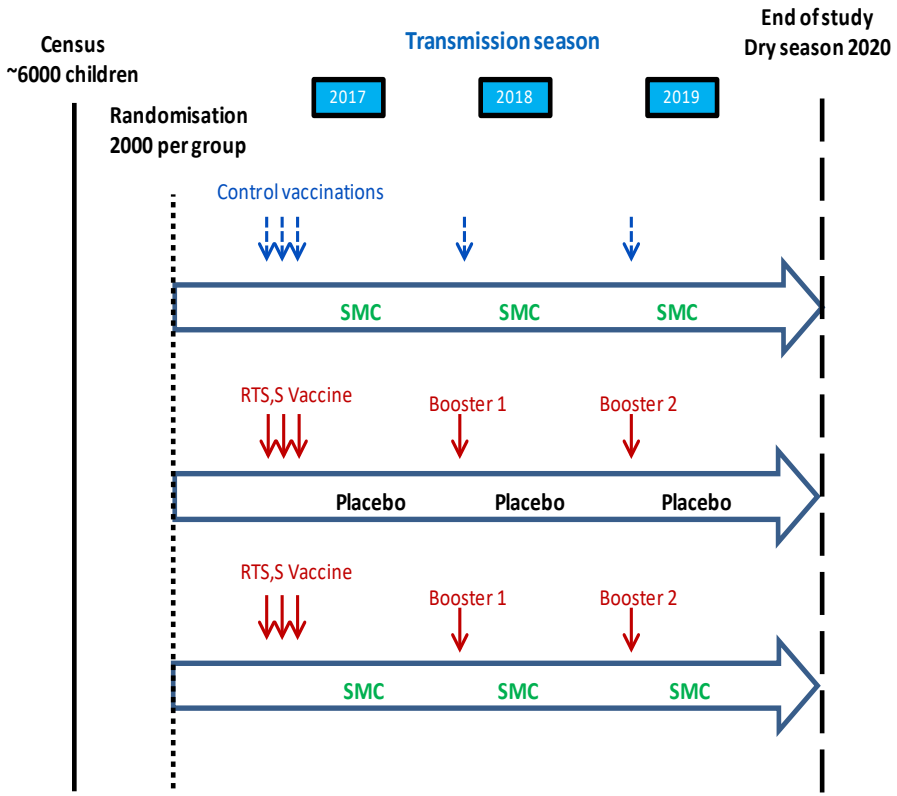
Only the combination of RTS,S-SMC has been evaluated in the context of a controlled trial

SMC: Seasonal Malaria Chemoprevention

Seasonal RTS,S vaccination

RTS,S-SMC trial, in Burkina Faso and Mali between 2017-2019 (Chandramohan et al., 2021)

Trial design



Summary results

- **Compared to SMC with 4 cycles per year, RTS,S provided non-inferior protection against clinical malaria**
- **A combined intervention of RTS,S and SMC is clearly superior**
  - **~ 60% reduction in primary outcome of clinical malaria**
  - **~ 70% reduction in WHO-defined severe malaria hospitalisations**
  - **~ 60% reduction in blood transfusions**
  - **~ 50% reduction in all cause deaths, excluding injuries and surgery**
  - **~ 70% reduction in deaths from malaria**

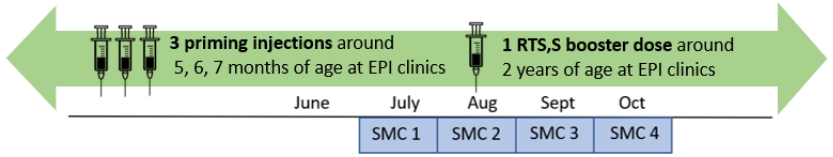
Countries may consider providing the RTS,S seasonally, with a 5-dose strategy in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks

BUT the high efficacy of the RTS,S seen in seasonal vaccination trial **will not be realized in practice** if the delivery approach is not optimal

How to optimize the Seasonal Vaccination ?

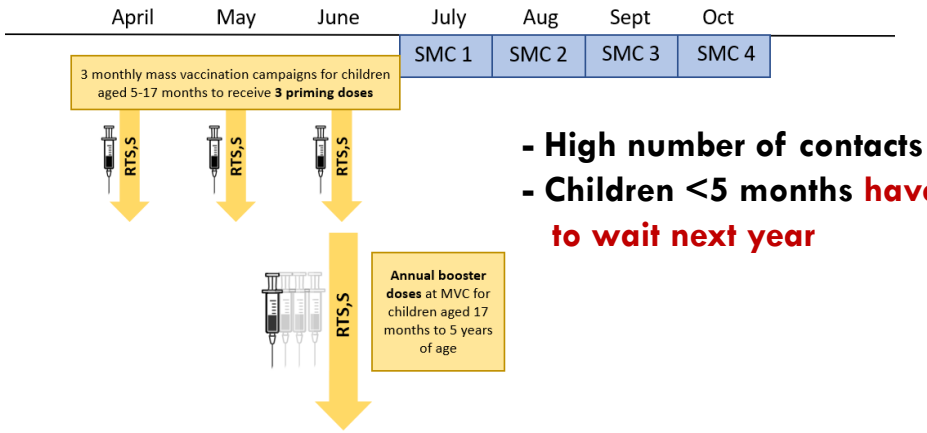
Possible strategies for RTS,S-SMC implementation

Strategy 1: Age-based routine EPI



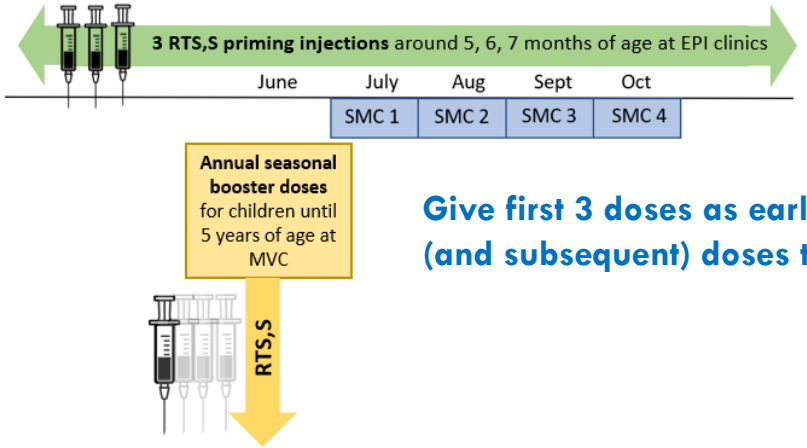
Doses are not optimally timed (unless born in the right month !)

Strategy 2: Seasonal mass vaccine campaigns



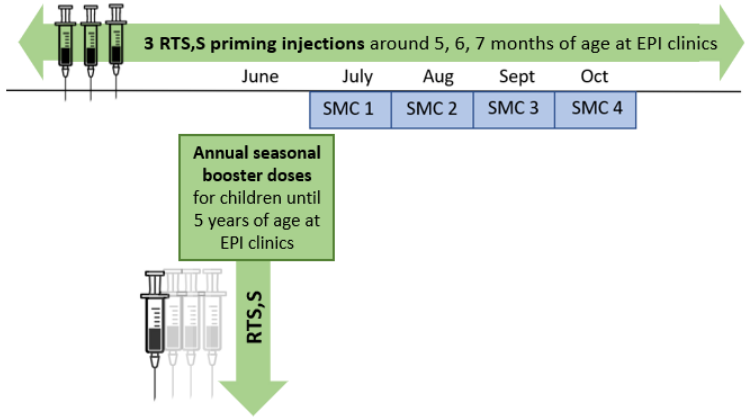
- High number of contacts
- Children <5 months have to wait next year

Strategy 3: Age-based and seasonal-mixed delivery systems



Give first 3 doses as early as possible (via EPI), and 4th (and subsequent) doses through seasonal campaigns

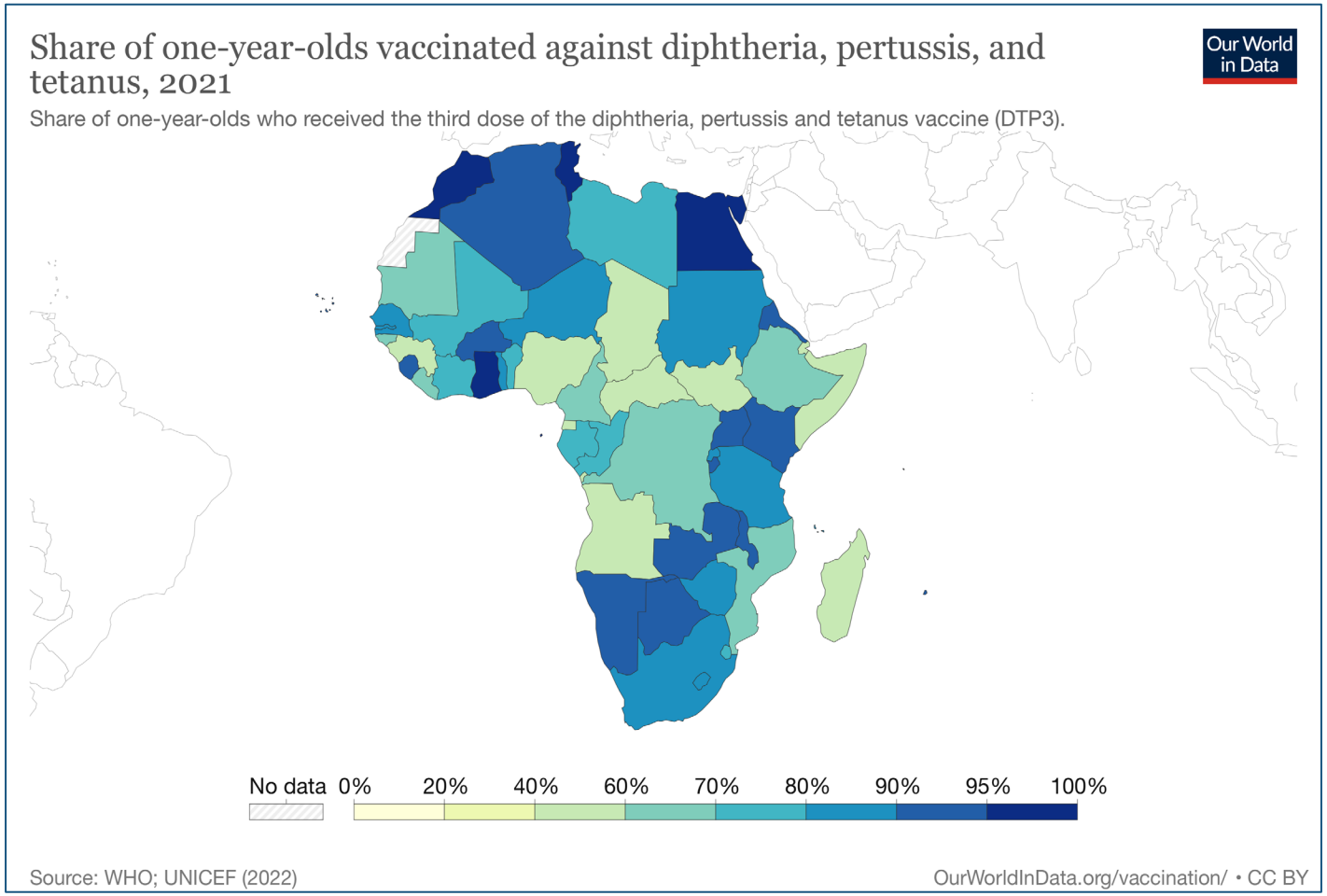
Strategy 4: Age-based and seasonal-routine EPI



RTS,S doses delivered via the routine EPI clinics | RTS,S doses delivered via mass vaccination campaigns | SMC cycle delivered by the NMCP

Some areas of implementation research ?

1. How to increase coverage in countries with low EPI coverage, but with high malaria burden ?
2. How to reduce the cost of mass campaigns (cost-effectiveness ?)
3. How to achieve 4 doses in nomadic populations and insecurity prone countries ?



Thank you …